REMARKS

The present Amendment is in response to the Examiner's Office Action mailed March 20, 2001. Claims 1-15, 19, 23, and 24 remain in this application. Claims 16-18 and 20-22 are canceled. Claims 44-50 are new. Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

1. Objections to the Claims

The Examiner objects to claim 8 for lacking a sequence identifier. Applicants amend claim 8 to include SEQ ID NO: 76 to identify the linker sequence. Withdrawal of this ground of objection is respectfully requested.

2. Rejections under 35 U.S.C. § 101

The Examiner rejects claims 1-24 under 35 U.S.C. § 101 on the ground that the claimed invention is not supported by either a specific and/or substantial asserted utility or a well-established utility. Specifically, the Examiner states that "[t]he claimed method for generating a library of yeast expression vectors, is not supported by a specific asserted utility and doe not, without further research and experimentation, provide an immediate benefit to the public". Applicants respectfully traverse the Examiner's grounds for utility rejection as being improper and unsupported.

Under the "Revised Interim Utility Guidelines" of the PTO, if at least one specific, credible, and substantial utility is provided, a rejection under 35 U.S.C. § 101 should not be made.

1) Specific Utility Provided

The claimed invention provides an efficient method for generating a library of yeast expression vectors which may then be used in a high throughput method for screening a diverse protein library against a specific target protein. The utility of the claimed method is based on the utility of the high throughput screening method described in the Specification in which the product of the presently claimed method is employed.

The high throughput method described in the Specification allows a diverse protein library to be rapidly and efficiently screened against a specific target protein. Classes and highly specific examples of target proteins including epidermal growth factors (EGFs), transferrin, insulin-like growth factor, transforming growth factors (TGFs), interleukin-1, and

interleukin-2 are provided in the Specification (See pp. 44-48, "The Target Proteins and Peptides"). Each target protein listed can be used in the claimed method for screening against the protein library. It is taught that the protein library may be a single-chain antibody, scFv which typical comprises a V_H domain and a V_L domain in polypeptide linkage. The proteins screened according to the method can be used in diagnostic applications for the target protein and as therapeutics for a specific disease associated with the target protein.

As taught in the Specification, antibodies identified through the method against a cell surface protein or receptor such as platelet glycoprotein IIb/IIIa receptor can be used to treat coronary artery disease. Antibodies identified through the method against CD4, CAMPATH-1 can be used to treat autoimmune diseases. See Specification, page 45, last paragraph. The myriad of specific utilities provided by the method of the present invention is endless.

To further demonstrate that a specific asserted utility has been provided, the Examiner's attention is drawn to original dependent claims 21-23 which recite specific disease associated proteins as target proteins. As can be seen from the originally claimed method, at least one specific utility has clearly been provided.

2) Substantial Utility Provided

A "substantial utility" is defined by the PTO Training Materials for the "Revised Interim Utility Guidelines" as a "real world" use. An assay method for identifying compounds that themselves have a "substantial utility" is considered to be a "real world" use.

As discussed above, the claimed method provides a product (i.e., a library of yeast expression vectors) which may then be used in a high throughput method for screening proteins, such as therapeutic antibodies, that can bind to specific disease-associated proteins. The resulting screened proteins can be used in diagnostic applications and for treating specific diseases in the clinic. Applicants therefore submit that a "real world" use demonstrating a substantial utility has also been provided.

3) Credible Utility Provided

The claimed method also has credible utility. It is well known that antibodies are widely used for the diagnosis and treatment of disease, the most celebrated one being HERCEPTIN® (Genentech Inc.) which has been shown to have substantial utility in treating breast cancer. Many commercial entities such as Cambridge Antibody Therapeutics use various screening methods such as phage display to select for therapeutic antibodies. A high throughput assay

for screening compounds such as therapeutic antibodies that can bind to specific disease associated proteins would be readily recognized to have credible utility as an alternative to phage display and other such screening methods for selecting therapeutic antibodies. Applicants therefore submit that the claimed method which provides yeast expression vectors for use in the highly useful screening assay is a credible utility.

In view of the specific, credible, and substantial utility of the claimed method, the pending utility rejection should be withdrawn.

3. Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner rejects claims 1-24 under 35 U.S.C. § 112, First Paragraph for insufficient written description and lack of enablement. The grounds for the Examiner's rejection are based on those for the rejection under 35 U.S.C. § 101. Specifically, the Examiner states that "since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention".

As discussed in Section 2 above, the Examiner's rejection under 35 U.S.C. § 101 is improper and unsupported and should be withdrawn. Given that the pending utility rejection is unsupported, the utility rejection cannot support the pending rejection under 35 U.S.C. § 112, First Paragraph. For this reason, Applicants respectfully request that the rejection under 35 U.S.C. § 112, First Paragraph be withdrawn.

4. Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 2-4, 16-18, and 21-22 under 35 U.S.C. § 112, Second Paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants address each of the indefiniteness rejections in detail below.

1) Claims 2 -4: the term "about"

Claims 2-4 are rejected as being indefinite on the grounds that the term "about" is not defined by the claim, the Specification does not provide standard for ascertaining the requisite degree, etc. Applicants amend claims 2-4 by deleting the term "about". Withdrawal of the rejection under 35 U.S.C. § 112, Second Paragraph is therefore respectfully requested.

2) Claims 16-18 and 21-22

Applicants' cancellation of claims 16-18 and 21-22 renders the rejection under 35 U.S.C. § 112, Second Paragraph moot.

5. Rejections under 35 U.S.C. § 103

1) Hoeffler, et al., Hua, et al. and Filpula et al.

The Examiner rejects claims 1-24 under 35 U.S.C. § 103(a) as being unpatentable over Hoeffler, et al. (1999, WO 99/28502), Hua, et al. (1997, Plasmid 38:91-96) and Filupa et al. (1998, WO 98/49198). Applicants traverse the Examiner's grounds for rejection for the reasons provided below.

Independent claim 1, as amended, specifies a method for generating a library of yeast expression vectors. The library is constructed **in vivo** by combining the inserts encoding a highly diverse library of single chain antibodies with a linearized yeast vector through homologous recombination of yeast cells. By exploiting the intrinsic ability of yeast cells to fill in the gap of a linearized vector with extremely high efficiency, a highly diverse library of single chain antibody having a diversity of at least $1x10^7$ was constructed efficiently and economically.

In contrast, Hoeffler, et al. teaches a method of constructing a library of yeast expression vectors **in vitro** through multiple subclonings and involving a series of vectors. See Hoeffler, et al., Claim 1, page 111. More specifically, Hoeffler, et al. teaches multiple steps of subclonings to ligate a scFv library to yeast expression vectors **in vitro**, eventually achieving a diversity of $3.6X10^6$. See Hoeffler, et al., examples at pages 52-55. This level of diversity of the library is considered by Hoeffler, et al. to be sufficient and was verified by fingerprinting amplified clones. See Hoeffler, et al., page 54, lines 5-7. As can be clearly seen from the cited passages, Hoeffler, et al. teaches a method of constructing a library of yeast expression vector via multiple subcloning steps **in vitro** at a lower diversity than what Applicants claim.

Hua, et al. merely teaches how to optimize homologous recombination in yeast by using terminal sequences having minimum length. See Hua, et al., Abstract. Nowhere does Hua, et al. teach or suggest the claimed method of constructing a library of yeast expression vectors encoding a highly diverse single chain antibody library. Hence, Hua, et al. fails to teach or suggest that there is a shortcoming in Hoeffler's in vitro construction approach or that Hoeffler's application would benefit from a higher level of diversity. Rather, the modification of Hoeffler, et al. to use homologous recombination to achieve more efficient in vivo construction and higher levels of diversity is purely the product of Applicants' inventive insight.

Filpula, et al. merely teaches how to synthesize a single-chain antibody capable of glycosylation. Specifically, amino acids required for glycosylation are specified in various positions of the single-chain antibody. See Filpula, et al., Abstract, and claim 1. As the Examiner acknowledges, Filpula et al. only describes the preferred range of the peptide linker being from 2 to 50 or 18 to 30 residues. Thus, Filpula et al. also fails to teach or suggest how to modify Hoeffler, et al. in order to arrive at the claimed method of constructing a library of yeast expression vectors.

Applicants' draw to the Examiner's attention Hoeffler's teaching that "[t]he diversity of the library doesn't need to be much above 10^6 since the transformation capacity of yeast is generally 10^7 or below". See Hoeffler, et al., page 54, lines 5-7. This teaching teaches away from the present invention and undermines any motivation to modify Hoeffler, et al. in order to achieve a higher level of diversity. Hence, absent some specific teaching in the other references cited that a higher level of diversity would be desirable in Hoeffler's technology contrary to Hoeffler's teaching away, the reliance upon Hua, et al. or Filpula, et al. to modify Hoeffler, et al. to achieve a higher level of diversity is unsupported and improper.

For the reasons provided above, Applicants submit that independent claim 1 is not rendered obvious by Hoeffler, et al. in combination with Hua, et al. and Filpula et al. under 35 U.S.C. § 103(a). Withdrawal of this ground of rejection is therefore respectfully requested.

2) Filpula et al., Hua, et al. and Hoeffler, et al.,

The Examiner rejects claims 1-24 under 35 U.S.C. § 103(a) as being unpatentable over Filupa et al., Hua, et al., and Hoeffler, et al. Applicants traverse the Examiner's grounds for rejection based on the following reasons.

As discussed above, independent claim 1 as amended specifies a method for generating a library of yeast expression vectors encoding a highly diverse library of single chain antibody. By comparison, the primary reference cited, Filpula et al., does not teach or suggest the claimed method of constructing a single chain antibody library having a diversity of at least $1x10^7$. Filpula et al. merely teaches how to synthesize single-chain antibody capable of glycosylation. Specifically, amino acids required for glycosylation are specified in various positions of the single-chain antibody. See Abstract, and claim 1. As the Examiner acknowledges, Filpula et al. only describes the preferred range of the peptide linker being from 2 to 50 or 18 to 30 residues. Thus, Filpula et al. fails to teach or suggest the claimed method of constructing a single chain antibody library with such a high diversity.

As also discussed above, Hua et al. neither teaches nor suggests the claimed method

of constructing a library of yeast expression vectors encoding a highly diverse single chain antibody library. Hua, et al. merely teaches how to optimize homologous recombination in yeast by using terminal sequences having minimum length. See Abstract.

Hoeffler, et al. meanwhile teaches away from the present invention by teaching a library with a diversity of only $3.6X10^6$ and further expressing satisfaction with the level of diversity achieved. Hoeffler, et al. effective teaches that yet higher levels of diversity are pointless, stating that "[t]he diversity of the library doesn't need to be much above 10^6 since the transformation capacity of yeast is generally 10^7 or below".

In view Hoeffler, et al.'s teaching away from the present invention, one of ordinary skill in the pertinent art would not be motivated to modify Filpula et al. in view of Hua, et al. and Hoeffler, et al. and arrive at the claimed invention. Applicants submit that independent claim 1 is not rendered obvious by these cited references under 35 U.S.C. § 103(a). Withdrawal of this ground of rejection is therefore respectfully requested.

3) Griffiths, et al. and Hua, et al.

The Examiner rejects claims 1-4 and 10-19 under 35 U.S.C. § 103(a) as being unpatentable over Griffiths, et al. (U.S. Patent No: 5,962,255) and Hua, et al. Applicants traverse the Examiner's grounds for rejection based on the following reasons.

Griffiths, et al. teaches a method of constructing **bacterial** expression vectors encoding single chain antibody library. This library of single chain antibodies are expressed by the bacterial expression vectors and displayed on the surface of secreted replicable genetic display packages (rgdps), e.g. filamentous phage. See Griffiths, et al., Abstract. To facilitate the phage display, multiple steps of cloning and bacterial transformation are involved. First, sequences encoding antibody heavy chain and light chain variable regions are inserted into phagemid vectors. Second, phagemid particle are produced and selected. Third, the selected phagemid particles are used to infect E. coli to generate clones which are selected by identifying positive clones by ELISA. See Fig. 2. Thus, Griffiths, et al. teaches a complete different system of library construction via phagemids.

Hua, et al. merely teaches how to optimize homologous recombination in yeast by using terminal sequences having minimum length. See Hua, et al., Abstract. Thus, Hua, et al. fails to teach the claimed method of constructing a library of yeast expression vectors encoding a highly diverse single chain antibody library.

In view of Griffiths' explicit requirement for producing phagemid particles for displaying the antibody library on their surface, replacing the system with a completely different expression

system such as yeast could not be reasonably be intended by Griffiths, et al. Such a dramatic replacement of the cloning and expression system would only destroy the function of the invention disclosed in Griffiths, et al. and render it inoperable. Thus, to one of ordinary skill in the art, there is no technological motivation for engaging in such a modification. To the contrary, there would be a disincentive.

For the reasons provided above, Applicants submit that independent claim 1 is not rendered obvious by these cited references under 35 U.S.C. § 103(a). Withdrawal of this ground of rejection is therefore respectfully requested.

CONCLUSION

In light of the remarks and arguments set forth above, Applicants earnestly believe that are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

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